CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS

Cladribine Activity in Adult Langerhans-Cell Histiocytosis

By Alan Saven and Carol Burian

Langerhans-cell histiocytosis (LCH) results from the clonal proliferation and accumulation of tissue histiocytes, clinically manifested as osteolytic lesions, hypothalamic insufficiency, and seborrheic and vesiculopustular lesions on the scalp, perineum, rectum, and vulva. The clinical presentation of LCH is characterized by the presence of multiple affected sites, which may include skin, bone, and lymph nodes. The diagnosis of LCH is established by identifying Langerhans or histiocytosis X cells, associated occasionally with multinucleated giant cells, in affected lymph nodes, bones, skin, and lungs by microscopy or immunohistochemical staining, such as positivity for the S-100 protein. Birbeck granules seen on electron microscopy and characterized by the indentation across the nucleus of mononuclear cells, are pathognomonic.

Treatment of LCH is principally palliative. The therapeutic modalities most frequently used are corticosteroids, alkylating agents, antimetabolites, vinca alkaloids, combination chemotherapy, irradiation, and immunotherapy. Cladribine (2-CdA) (cladribine, Leustatin [Ortho Biotech, Raritan, NJ]), a purine analogue with activity in indolent lymphoproliferative disorders and myeloid leukemias, is potently toxic to monocytes in vitro. Cladribine was approved by the Food and Drug Administration (FDA) in 1993 for the treatment of hairy cell leukemia, an uncommon chronic B-cell lymphoproliferative disorder characterized by mononuclear cells displaying cytoplasmic projections, as single courses of treatment induce long-lasting complete remissions in the vast majority of patients treated. Because tissue histiocytes and circulating monocytes have common progenitor cell origins, cladribine was a rational therapeutic option. Previously, we reported on three patients with LCH, all of whom obtained complete and durable remissions after cladribine administration. We, therefore, conducted a phase II study evaluating the efficacy and toxicity of cladribine in larger numbers of patients with LCH.

MATERIALS AND METHODS

Eligibility Criteria

Patients were required to have a histologic diagnosis of LCH with clinically or radiologically measurable disease and symptoms. The histopathologic diagnostic criteria used were those previously proposed by the Writing Group of the Histiocyte Society. Definitive diagnosis required the finding of Birbeck granules in lesional cells by electron microscopy or demonstration of CD1a antigenic determinants on the surface of lesional cells. Diagnosis was justified when the lesion was characteristic by light microscopy and the lesional cells showed the presence of two or more of the following features: positive stain for adenosine triphosphatase (ATPase), S-100 protein, or alpha-D-mannosidase or characteristic binding of peanut lectin in lesional cells. Presumptive diagnosis was warranted when findings, on study of conventionally stained biopsy material alone, were merely "consistent" with those defined in the literature. All pathologic materials were reviewed by the pathologists at Scripps Clinic.

Patients could have received prior chemotherapy, steroids, radiation therapy, red blood cell or platelet transfusion support, but had to be off chemotherapy or radiation therapy for more than 4 weeks. Adequate renal (serum creatinine < 2.0 mg/dL) and hepatic function (bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) < 2 times normal) were required. Patients also had to be at least 15 years of age and assessable for follow-up.

Approval was obtained from the Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

Baseline and Follow-Up Studies

Before the initiation of cladribine, patients underwent a complete history and physical examination, complete blood count with differentials, and standard diagnostic studies including liver and renal function tests, complete blood count, urinalysis, and chest radiographs. Bone scan, CT scan, and MRI were performed for patients with bone involvement. At each visit, a complete blood count, urinalysis, and liver and renal function tests were performed. Additional tests were performed as indicated by clinical need. When the frequency of any test was at the discretion of the treating physician.

From the Division of Hematology/Oncology, Ida M. and Cecil H. Green Cancer Center, Scripps Clinic, La Jolla, CA.

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Address reprint requests to Alan Saven, MD, Head, Division of Hematology/Oncology, MS217, Scripps Clinic, 10666 North Torrey Pines Rd, La Jolla, CA 92037; e-mail: asaven@scrippsclinic.com.

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In Table 1. Of the 13 patients treated, seven were men and six were women. The median age at initiation of cladribine was 42 years (range, 19 to 72 years) and the median pretreatment duration was 99 months (range, 6 to 252 months). Using the histopathologic diagnostic criteria proposed by the Writing Group of the Histiocyte Society, five patients had a definitive diagnosis, four had a diagnosis and four had a presumptive diagnosis of LCH.10 One patient had received no prior therapy, one patient had received prior prednisone, one patient radiation only, six patients radiation and chemotherapy, and four patients surgery, radiation, and chemotherapy. Using the staging system as designated by Lavin and Osband,19 eight patients had stage I disease, four patients stage II disease, and one patient had stage III disease. The sites of active disease before the initiation of cladribine was skin in seven patients, bone (all multifocal) in six patients, lung in four patients, soft tissue in two patients, and lymph nodes in two patients. Four patients had prior diabetes insipidus, two patients had loss of teeth from gingival involvement, and two patients had marked pulmonary fibrosis. Patients 1 and 2 have been previously reported,14,15 as have been the pretreatment characteristics of patient 12.20

Response Criteria
A complete response was defined as the absence of active disease on physical examination and imaging studies.17 Disease activity was established on clinical grounds.17 Active disease was defined as chronic progression, new symptomatic, histologically verified organ manifestations or local disease recurrence after initially successful therapy. Inactive disease was defined as no lesion/disease, stable asymptomatic, or stable symptomatic, but not progressive disease. Cutaneous lesions did not require repeat biopsy to document histologic resolution. A partial response was defined as a reduction by more than 50% of all measurable and active disease for more than 1 month. Any response less than partial was designated as no response. All clinical assessments were made by the author (A.S.), and all imaging studies were reviewed by the radiologists at Scripps Clinic.

Cladribine Therapy
Cladribine was administered at 0.1 mg/kg daily for 7 days by continuous intravenous infusion (patients 1 and 2) and 0.14 mg/kg per day over 2 hours intravenously daily for 5 consecutive days (patients 3 to 13), with courses repeated every 4 weeks, toxicity permitting. If, 4 weeks after the completion of the third course of cladribine, the patient did not achieve a partial or complete response, then no further cladribine was administered. The patient was then switched to alternative therapy if deemed appropriate. If, 4 weeks after the completion of the third course of cladribine a partial response had been achieved, cladribine was administered until maximum response or prohibitive toxicity was encountered. If a complete response had been achieved, then the patient received no further cladribine until documented disease recurrence, when this occurred. The total number of courses of cladribine administered did not exceed a maximum of six courses.

Toxicity
The National Cancer Institute Common Toxicity Criteria were used for the evaluation of toxicity with grade 3 and 4 being considered significant.18 The initiation of cladribine therapy was delayed for an absolute granulocyte count < 1.0 × 10^9 per liter, or a > 50% reduction in the pretreatment platelet count. Cladribine was then held until the platelet count was more than 75% of the pretreatment value, or if the platelet count was > 100 × 10^9 per liter, cladribine could be administered regardless.

RESULTS

Patient Characteristics
Patient characteristics at the initiation of cladribine are shown in Table 1. Of the 13 patients treated, seven were men and six were women. The median age at initiation of cladribine was 42 years (range, 19 to 72 years) and the median pretreatment duration was 99 months (range, 6 to 252 months). Using the histopathologic diagnostic criteria proposed by the Writing Group of the Histiocyte Society, five patients had a definitive diagnosis, four had a diagnosis and four had a presumptive diagnosis of LCH.10 One patient had received no prior therapy, one patient had received prior prednisone, one patient radiation only, six patients radiation and chemotherapy, and four patients surgery, radiation, and chemotherapy. Using the staging system as designated by Lavin and Osband,19 eight patients had stage I disease, four patients stage II disease, and one patient had stage III disease. The sites of active disease before the initiation of cladribine was skin in seven patients, bone (all multifocal) in six patients, lung in four patients, soft tissue in two patients, and lymph nodes in two patients. Four patients had prior diabetes insipidus, two patients had loss of teeth from gingival involvement, and two patients had marked pulmonary fibrosis. Patients 1 and 2 have been previously reported,14,15 as have been the pretreatment characteristics of patient 12.20

Responses and Response Duration
Of the 13 patients treated, 12 were evaluable for response and all for toxicity. Patient 11, invaluable for response, received only a single course of therapy and was not seen in follow-up. After a median of three courses of cladribine (range, 1 to 6), seven (58%) patients achieved complete responses (two pathologic and five clinical) and two (17%) patients partial responses, for an overall response rate of 75% (95% confidence interval, 43% to 95%). Three (25%) patients had stable disease and were scored as nonresponders. The median response follow-up duration was 33 months (range, 1 to 65+ months); the median follow-up response duration for complete responders was 33+ months (range, 1 to 65+ months), and the response follow-up duration for the partial responders was 36+ and 8+ months.

Individual patient responses and their duration are shown in Table 2. The cutaneous responses of patients 6 and 12 are shown in Figs 1 and 2. The pretreatment CT scan of the abdomen and pelvis in patient 6 showed asymmetric enlargement and facial plane effacement of the musculature of the left buttocks, including the gluteal, pyriformis, obturator, and internus muscles, with extension through the sciatic notch and encroachment into the fat of the left ischiorectal fossa. After cladribine, there was complete resolution with the absence of asymmetry on CT scan.

Toxicities, Late Events, and Survival
The principal acute toxicity was hematologic with seven patients experiencing grade 3 or 4 neutropenia (Table 2). In two of these seven patients, neutropenia was complicated by fever necessitating hospital admission for intravenous antibiotics. In both patients, cultures remained negative. No patients experienced grade 3 to 4 anemia or grade 3 to 4 thrombocytopenia. Patient 11, with a history of a seizure disorder, experienced chills, tightness in his chest, wheezing, hyperventilation, hypertension, and became briefly cyanotic after the acute administration of cladribine. It resolved spontaneously without treatment, and it is unknown if this event was related to cladribine or if the patient had experienced a seizure. Only a single patient, patient
1, had a documented infection, dermatomal herpes zoster, which occurred soon after the first course of cladribine and resulted in a delay in the second course. The course of patient 6 was complicated by diarrhea, which resolved spontaneously without therapy. Patient 1 with a prior history of papillary carcinoma of the thyroid had disease recurrence 4 years after cladribine therapy. She had a preceding history of papillary carcinoma of the thyroid having undergone a resection for this 2

Table 1. Pretreatment Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex (yrs)</th>
<th>Pretreatment Disease Duration (mos)</th>
<th>Pathologic Diagnosis</th>
<th>Prior Therapy</th>
<th>Stage at Start of Cladribine</th>
<th>Sites of Disease Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33/F</td>
<td>204</td>
<td>Presumptive</td>
<td>Prednisone, vinblastine, azathioprine, VP-16, methotrexate, Radiation</td>
<td>I</td>
<td>Skin, external auditory canals, mouth, vagina, diabetes insipidus</td>
</tr>
<tr>
<td>2</td>
<td>57/M</td>
<td>7</td>
<td>Definitive</td>
<td>Prednisone</td>
<td>II</td>
<td>Skin, neutropenia</td>
</tr>
<tr>
<td>3</td>
<td>20/M</td>
<td>176</td>
<td>Presumptive</td>
<td>Prednisone, vinblastine, suppressin A (experimental), VP-16 C5 vertebrectomy</td>
<td>I</td>
<td>Bone (vertebrae, orbits, skull, sternum, ribs and pelvis)</td>
</tr>
<tr>
<td>4</td>
<td>50/M</td>
<td>21</td>
<td>Presumptive</td>
<td>Prednisone</td>
<td>I</td>
<td>Bone (mandible and ribs), gingiva, tooth loss, lung</td>
</tr>
<tr>
<td>5</td>
<td>42/F</td>
<td>133</td>
<td>Diagnosis</td>
<td>Prednisone, vinblastine Radiation Bowel resection, partial hepatic resection</td>
<td>I</td>
<td>Skin, mouth, vagina, colon, diabetes insipidus</td>
</tr>
<tr>
<td>6</td>
<td>35/M</td>
<td>99</td>
<td>Diagnosis</td>
<td>Topical nitrogen, mustard, VP-16 Electron beam radiation</td>
<td>I</td>
<td>Skin, soft tissue, diabetes Insipidus, pulmonary</td>
</tr>
<tr>
<td>7</td>
<td>72/M</td>
<td>34</td>
<td>Definitive</td>
<td>Prednisone, cyclophosphamide Radiation</td>
<td>I</td>
<td>Skin</td>
</tr>
<tr>
<td>8</td>
<td>47/M</td>
<td>114</td>
<td>Definitive</td>
<td>Radiation</td>
<td>II</td>
<td>Bone (mandible and maxilla), lung, edentulous</td>
</tr>
<tr>
<td>9</td>
<td>37/M</td>
<td>22</td>
<td>Diagnosis</td>
<td>Prednisone, vinblastine Radiation Percardiecomy</td>
<td>III</td>
<td>Bone (mandible, radius and ribs), soft tissue, lung, lymphadenopathy, ascites, diabetes insipidus</td>
</tr>
<tr>
<td>10</td>
<td>68/F</td>
<td>64</td>
<td>Diagnosis</td>
<td>Vinblastine, methotrexate, 6-thioguanine Radiation</td>
<td>I</td>
<td>Skin, mouth, vagina, anemia</td>
</tr>
<tr>
<td>11</td>
<td>34/M</td>
<td>146</td>
<td>Definitive</td>
<td>Vinblastine, vincristine, interferon, methotrexate, VP-16, prednisone Radiation</td>
<td>II</td>
<td>Bone (skull, hips, vertebrae, clavicle,ibia and ribs), lung</td>
</tr>
<tr>
<td>12</td>
<td>46/F</td>
<td>253</td>
<td>Definitive</td>
<td>Vinblastine, methotrexate, isotretinoin, interferon Radiation</td>
<td>I</td>
<td>Skin</td>
</tr>
<tr>
<td>13</td>
<td>19/F</td>
<td>6</td>
<td>Presumptive</td>
<td>None</td>
<td>II</td>
<td>Bone (skull, femur, fibula and pelvis), lung, lymphadenopathy</td>
</tr>
</tbody>
</table>

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Table 2. Cladribine Treatment Outcomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Response</th>
<th>Response Duration (mos)</th>
<th>No. of Cladribine Courses</th>
<th>Toxicities/Late Events</th>
<th>Status (follow-up in months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>65+</td>
<td>4</td>
<td>Grade 4 neutropenia with fever Recurrence of papillary carcinoma of thyroid</td>
<td>Alive (76)</td>
</tr>
<tr>
<td>2</td>
<td>CR</td>
<td>36</td>
<td>2</td>
<td>Chronic myelomonocytic leukemia</td>
<td>Dead (41)</td>
</tr>
<tr>
<td>3</td>
<td>NR</td>
<td>—</td>
<td>3</td>
<td>Grade 3 neutropenia</td>
<td>Alive (39)</td>
</tr>
<tr>
<td>4</td>
<td>CR</td>
<td>46+</td>
<td>2</td>
<td>Grade 4 neutropenia</td>
<td>Alive (49)</td>
</tr>
<tr>
<td>5</td>
<td>CR (Pathologic)</td>
<td>5</td>
<td>3</td>
<td>Alive (47)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CR</td>
<td>33+</td>
<td>6</td>
<td>Grade 3 neutropenia</td>
<td>Alive (48)</td>
</tr>
<tr>
<td>7</td>
<td>CR (Pathologic)</td>
<td>1</td>
<td>6</td>
<td>Alive (47)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CR</td>
<td>10+</td>
<td>6</td>
<td>Alive (45)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PR</td>
<td>36+</td>
<td>6</td>
<td>Grade 4 neutropenia with fever</td>
<td>Alive (42)</td>
</tr>
<tr>
<td>10</td>
<td>NR</td>
<td>—</td>
<td>2</td>
<td>Grade 4 neutropenia</td>
<td>Alive (32)</td>
</tr>
<tr>
<td>11</td>
<td>NE</td>
<td>—</td>
<td>1</td>
<td>Possible acute allergic reaction to cladribine</td>
<td>Alive (16)</td>
</tr>
<tr>
<td>12</td>
<td>PR</td>
<td>8+</td>
<td>6</td>
<td>Grade 4 neutropenia</td>
<td>Alive (15)</td>
</tr>
<tr>
<td>13</td>
<td>NR</td>
<td>—</td>
<td>3</td>
<td>Alive (6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; NR, no response; NE, not evaluable.
years before institution of cladribine therapy. Patient 2 developed chronic myelomonocytic leukemia 38 months after cladribine therapy. Bone marrow cytogenetics showed a normal male karyotype.

At a median follow-up of 42 months (range, 5 to 76), 12 patients remain alive and one patient (patient 2) has died.

DISCUSSION

This phase II study has demonstrated that single-agent cladribine has major activity in the treatment of adults with LCH, and this was achieved with a favorable toxicity profile. Responses were documented in patients with cutaneous, oral, osseous, soft tissue, lymph node, and pulmonary sites of involvement. The majority of responses were complete, generally durable, and unmaintained. These results confirm and extend the observations made previously in three adults with LCH treated with cladribine.14,15

Other investigators have also reported in small numbers of patients on the successful application of cladribine to the treatment of LCH.21,22 Dimopoulos et al23 administered cladribine to a 34-year old patient with LCH who was resistant to corticosteroids and etoposide. After four courses of cladribine, the patient achieved a complete remission, which was ongoing for 12 months. Stine et al24 reported on three children with

Fig 1. The inguinal area of patient 6 is shown before (A) and after (B) six courses of cladribine. Pretreatment, the area shows active cutaneous lesions, serosanguineous, and pustular drainage, which has resolved after treatment.

Fig 2. These photographs show the purple-colored, nodular cutaneous lesions of patient 12. Her face, with the nasal disfigurement, and her right shoulder is shown before (A and C) and after six courses of cladribine therapy (B and D).
LCH, all of whom achieved complete responses after cladribine therapy. As expected, myelosuppression was the principal toxicity.

Cladribine is an antimetabolite that uniquely destroys resting and dividing lymphocytes equally. 25 It is also potently toxic to monocytes, 13 which may explain its potential application to the treatment of monocyte-derived neoplasms and chronic inflammatory conditions, like multiple sclerosis. 26, 27 A further potential mechanism of action of cladribine in LCH may be through T-cell depletion, as cladribine is potently immunosuppressive. 28, 29 It is thought that the activity of cyclosporine in LCH is mediated through its immunosuppressive effects. 30 It should be noted that children with congenital adenosine deaminase deficiency, in which there is only an absence or immunologic incompetence of lymphocytes, do not have monocytopenia. 31 Additionally, 2'-deoxycoformycin, a tight-binding inhibitor of adenosine deaminase that in some ways simulates the defects of severe combined immunodeficiency disease and has a similar spectrum of activity against indolent lymphoproliferative disorders as that of cladribine, is not toxic to monocytes. 32

Because cladribine is powerfully immunosuppressive, reducing CD4 lymphocytes for up to 2 years and its incorporation into DNA is potentially mutagenic, 25, 33 it was speculated that cladribine might be responsible for an increased incidence of second cancers. 29, 34 A long-term follow-up study at Scripps Clinic of patients with hairy cell leukemia treated with cladribine identified an observed-to-expected ratio of second malignancies of 1.88 (95% confidence interval, 1.24 to 2.74), a small but statistically significant increase. 35 Multiple other investigators have also investigated cladribine treatment in hairy cell leukemia and the incidence of second malignancies and have failed to establish such a causal relationship. 36, 37 It is thought that patients with hairy cell leukemia have an intrinsic susceptibility to developing second cancers, which is made manifest by the improved survivals that these patients now enjoy. In this report of cladribine use in adults with LCH, one patient developed chronic myelomonocytic leukemia and one patient had recurrence of papillary carcinoma of the thyroid gland. As has been described for hairy cell leukemia, a high incidence of associated malignancies has been documented in patients with LCH, including myelomonocytic leukemia, 13 which could precede, be coincidental with, or occur after a diagnosis of LCH. 28 It should be emphasized that patients with hairy cell leukemia generally receive only a single course of cladribine treatment, while in this study, patients with LCH received a median of three courses of cladribine (range, 1 to 6). The multiple courses of cladribine might have a different effect on the incidence of second malignancies. Obviously, determination of potential long-term risks will require continued and meticulous follow-up of treated patients.

Thus, cladribine has significant activity in adults with LCH and warrants further investigation both as a single agent and in combination with other drugs in pediatric and adult LCH, as well as other histiocytic syndromes. Prospective randomized studies are now warranted to determine the role of cladribine in patients with LCH at relapse or even as front-line therapy in high-risk patients. The subcutaneous and oral bioavailability of cladribine will further facilitate its administration to patients with LCH. 39, 40

REFERENCES


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